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Description

Microfluidics Packaging

Cross Reference to Related Applications

[0001] This application relates to the invention described in Attorney Docket Number FIS920020187US1, incorporated herein by reference in its entirety.

Background of Invention

[0002] TECHNICAL FIELD

[0003] The field of the invention is that of simultaneously testing many compounds for biological/chemical interactions. In particular, the current invention is a device / structure and a method to test drug interactions.

[0004] In order to improve the efficiency of drug discovery, leading pharmaceutical companies have implemented high-throughput screening (HTS) techniques for the evaluation of potential drug candidates. In high throughput screening, a reagent set A (for example, a biological target with appropriate assay reagents) is tested for reactivity with chemicals B1--Bn (for example, compounds taken from a

molecular library), where n can be a large number, on the order of millions. High-throughput screening can enable the testing of large numbers of compounds rapidly and in parallel. Current efforts are standardized around the use of plastic consumables known as microtiter plates, or microplates. A set of substances B1-Bn can be arrayed in these microplates, and then reagent set A, which could include chemicals that test for the interaction with a specific biological target, can be mixed with each of the Bn. Detector instrumentation, for example, optical microplate readers, can then be used to detect interactions.

[0005] The pharmaceutical industry currently has a need for improvements in high-throughput screening technology to improve drug-discovery efficiency and to keep costs down. Reagents and compounds used in drug discovery are often scarce and expensive, which has prompted the development of miniaturized assays with smaller assay volumes. Microtiter plates are commercially available in a variety of standard well formats (e.g. 96;, 384;, and 1536 wells per plate), with well dimensions typically on the order of a few to several millimeters. Assays performed in these plates typically use in excess of ten microliters of reagent per test point. These types of reactions could the-

oretically be performed with sub-microliter volumes of reagents, but to date such low-volume assays have not achieved widespread adoption. One significant factor inhibiting the adoption of low-volume assays is the lack of methods for reliable high-performance fluid delivery.

[0006] Recently, "Autonomous Microfluidic Capillary System" David Juncker, Heinz Schmid, Ute Drechsler, Heiko Wolf, Marc Wolf, Bruno Michel, Nico de Rooij, and Emmanuel Delamarche, Anal. Chem.; 2002; 74(24) pp 6139; 6144; has described a specific design concept to regulate the flow of multiple reagents in a capillary-driven microstructure. In this concept, the flow of a reagent is initiated by its delivery to a service port and then terminates when the fluid has drained to the point where the trailing meniscus has reached an element known as a capillary retention valve. Flow rates during this phase can be controlled by engineering the geometry and surface characteristics of the microstructure.

[0007] The art has been able to provide some control over the position of the liquid in a microstructure, but the user is required to deposit the correct amount of fluid into the service port, with a high degree of accuracy. One of the difficulties in moving to smaller and smaller amounts of

liquid is the ability to meter out precise quantities of liquid for delivery into the service port using conventional means. A method is needed whereby the microstructure can actually improve the delivery of fluid instead of merely acting as a receiver.

[0008] Arrays of wells are carried by robotic handlers from one instrument to another.

[0009] The industry has combined, e.g. in the Microplate Standards Committee of the Society for Biomedical Screening, 36 Tamarack Avenue, Danbury CT 06811, to specify mechanical dimensions for multi-well plates.

SUMMARY OF INVENTION

[0010] The invention relates to a ceramic device with micro wells and micro channels and a method for formation thereof.

[0011] A feature of the invention is the fabrication of an array of micro wells and micro channels in a ceramic structure by laminating multiple personalized green sheets.

[0012] In one aspect of the invention, the open wells and channels are formed by individual layer personalization.

[0013] In another aspect of the invention, the array comprises U-shaped channels with vertical branches having different diameters.

[0014] In another aspect of the invention, fluid delivery in the

channels is controlled with engineered geometries in the channels.

[0015] In another aspect of the invention, fluid delivery is controlled by parameters of various surfaces and/or surface features like roughness.

[0016] In another aspect of the invention, self-metering of fluid volume is achieved by use of differential capillary forces.

[0017] Another feature of the invention is the use of a sacrificial material that escapes from the ceramic structure during the sintering process.

[0018] Another aspect of the invention is the control of the channel volume during sintering process.

[0019] Another aspect of the invention relates to an interface/holder for a sample plate with micro wells for holding samples to be tested that holds the plate while operations are performed on the wells.

[0020] Another feature of the invention is the provision of a set of supports in mechanical contact with the plate being held and a set of adjusters for moving the plate and supports relative to a supporting frame.

[0021] Another feature of the invention is an array of interface modules matching the array of sample holders for applying gaseous pressure to the sample holders.

[0022] Another feature of the invention is the provision of an array of two types of interfaces positioned in alternation, so that a first type can be applied to a first subset of the array and a second type can then be applied to the same subset by translating the array.

[0023] Another feature of the invention is the provision of means for optically inspecting the sample holders interspersed with means for applying gaseous pressure to the sample holders.

Brief Description of Drawings

[0024] Figure 1 shows a general view of an embodiment of the invention together with a holder for the embodiment.

[0025] Figure 2 shows a top view of an array.

[0026] Figure 3 shows a detail of a sub-array.

[0027] Figure 4A shows a top view of an individual module of an array.

[0028] Figure 4B shows a cross section of the module of Figure 4A.

[0029] Figures 5A; 5G show steps in the assembly of an embodiment of the invention.

[0030] Figure 6 shows a step in fluid delivery.

[0031] Figures 7A; 7D show transfer control implemented by sur-

face parameters.

[0032] Figures 8A; 8G illustrate steps in a sequence of operations that transfer a defined quantity of reagent.

[0033] Figure 9A shows a top view of an embodiment of the invention.

[0034] Figure 9B shows a cross section of the module of Figure 4A.

[0035] Figure 10 shows a detail of an assembly of an embodiment of the invention.

[0036] Figure 11 shows an arrangement adapted for optical inspection of the array.

[0037] Figure 12 shows an alternative array adapted for optical inspection and mechanical manipulation.

[0038] Figure 13 shows an exploded view of a detail of a holder according to the invention.

DETAILED DESCRIPTION

[0039] Fig. 1 shows a perspective view of an embodiment of the invention together with a holder/carrier for it. Card 100, according to the invention, is a relatively thin plate containing an array of fluid containers that contain a set of samples to be tested. The overall dimensions of card 100 are in compliance with an industry standard, as are the location of the individual modules within the array.

[0040] Card 100 fits into holder 10, which positions it, has available vacuum and pressure for fluid control and adapts to a robotic material handling apparatus.

[0041] Figure 2 shows a top view of an array 100 according to the invention. The industry has defined specifications for standard arrays, though non-standard arrays may be used if preferred. In this case, the array is a set of 48x32 sub-modules, each of the sub-modules containing a 2x2 sub-array of unit modules. On the lower right of the Figure, a sub-module 110 contains four unit modules 110;1 110;4 that are illustrated in the following Figures.

[0042] Figure 3 shows a detail of a sub-module 110, containing four unit modules 110-1; 110-4. Each unit module contains a U-shaped channel with one larger input branch and one smaller output branch. For example, the input branch has a top diameter denoted by a circle 122 and a vertical passage 121. The output branch has a top diameter 124 and a vertical passage 123. The diameter of passage 123 is shown as being the same diameter for convenience in the drawing, but may be less than the corresponding diameter of passage 121. The sizes of the branches and surface materials of the branches are chosen as described below, to control fluid motion and posi-

tion.

[0043] One novel example of the use of U-shaped geometries to help achieve reproducible microfluidic device performance stems from their ability to help prevent the introduction of undesired bubbles into the active device regions of a microfluidic structure.

[0044] The invention takes advantage of microfluidic separation by gravity, relying on the fact that bubbles that are introduced at the input of a device will float up to the top. So a geometry that allows bubbles to float to the top and where the bubble-free fluid can then be directed downward to the active device areas assists in excluding bubbles from active regions. The use of U-shaped structures is one method to prevent bubble incorporation into the microchannel. Other methods such as size-exclusion filters can be implemented in conjunction with this approach to assist in the removal of bubbles from specified areas.

[0045] Figure 4A shows a top view of a single sub-module of the array in Figure 2. Figure 4B shows a cross section of the structure of Figure 4A, formed using 6 green sheets and 1 horizontal channel connecting two vertical wells for simplicity in illustration. It should be noted that both vertical

wells and horizontal channels can be formed in a single layer or by combination of multiple layers in a suitable material, like ceramic, organic, glass, metal, or composite. The structure shown in Figure 4 has been assembled from individual sheets by lamination. The assembly process is the same for ceramic structures with arrays of thousands of unit modules, with thousands of horizontal channels selectively connected to link vertical holes. The ceramic material may include alumina, glass ceramic, aluminum nitride, borosilicate glass and glass. The diameter of vertical wells 121, 123 can be 20 microns or more, the channel width 126 can be 20 microns or more and the length can be a minimum of two diameters/40 microns. The foregoing dimensions are illustrative and may decrease as technology improves. The shape of a well exposing a substance may be circular, rectangular, smooth or rough. The total thickness of the plate 100 may be any desired amount, but preferably is under 1 mm. The thickness of an individual greensheet depends on the application, but preferably is about 150 microns.

[0046] The lamination process involves heat, pressure and time. The preferred lamination pressure is under 800 psi, the temperature is under 90 deg C and for a time of less than

5 minutes. The sintering process involves the material of choice and the binder system used to form the green-sheets.

[0047] The sintering process could include temperatures less than 2000C, and can be isostatic, free, and/or conformal. The ambient includes air, nitrogen, hydrogen, steam, carbon dioxide, and any combinations thereof.

[0048] The diameter of channels used in fabrication will depend on the particular application and technical variables such as the viscosity of the substance passing through, the surface tension/activity of the surface and fluid, desired flow force, capillary or forced flow, desired quantity and rate of flow, etc.

[0049] According to one example of the invention, the green-sheets are formed from a substance such as alumina, glass, ceramic and glass and ceramic, referred to as ceramic greensheets. The technique for forming vertical apertures and horizontal channels is material removal by mechanical techniques such as punching the material out, laser drilling, e-beam drilling, sandblasting and high pressure liquid jets. Some applications may employ channels formed by non-material removal techniques such as embossing, pressing, forming, and casting.

[0050] Figure 4B shows a portion of a simplified completed structure according to the invention, formed of six layers and having a single horizontal channel 126 formed in a sheet 130-5 and connecting two vertical apertures 121 and 123 formed in sheets 130-2, 130-3 and 130-4. The sheets 130-i were initially separate ceramic greensheets that have been laminated and sintered in a conventional process to form ceramic plate 100. At the top, different sized apertures described below are used for input of fluid reagents and for input of another reagent that combines to form the sample or for application of the test compound for the test of the compound.

[0051] In one embodiment of the invention, the layer that contains the bottom surface of the horizontal channel 126 has the bottom surface of the channel adapted for holding sample material, e.g. reaction products. The surface may have a minimum roughness (of less than 1 micron, say), and/or be shaped with a depression to contain the material during handling. In addition, the layer should be adapted for high speed scanning, e.g. be thin enough to fit in conventional scanners, have the cells placed close enough together to minimize time spent traveling from one to another, etc. Figure 4B shows a version in which

the top surface 125 upon which reaction products will deposit (and that forms the bottom of the U-shaped structure) is in a solid bottom layer 130-6 and the aperture is formed in a lower layer 130-5 that rests on the bottom layer. An alternative in which aperture 126 is formed as a groove in the bottom layer may also be used.

[0052] Preferably, the layer containing the top surface 125 upon which reaction products will deposit (and that forms the bottom of the U-shaped structure) is removable; i.e. it adheres to the upper layers well enough to keep the fluids from leaking, but can easily be separated from the upper layers. The method of attachment may be any known in the art, e.g. heat, tape, a pressure-sensitive sealant, or silk-screening a sealing material.

[0053] In operation, a reagent is inserted (using a pipette for example) in aperture 122, then is attracted by the increased capillary force caused by the decrease in diameter down to passage 121. The reagent is drawn in for a set time after which the dispensing pipette is withdrawn.

[0054] When the reagent reaches the bottom of passage 121, it travels horizontally until it reaches passage 123, where it rises up to a level that may be influenced by various means described below.

[0055] Referring to Figure 8, the fluid can be effectively self-metered from an external fluid reservoir (as one example, we can use a conventional pipette tip), by designing a system whereby the structure works in conjunction with the fluid reservoir. This requires some limited knowledge of the external fluid reservoir's geometry, dimensions, and surface-wettability characteristics. The microstructure provides capillary pressure to draw in fluid by a combination of diameter and surface properties such that the capillary force pulling fluid into the reservoir is greater than the force keeping it in the pipette.

[0056] One embodiment provides a flow-resistance element to control the rate of fluid extraction. In typical use, the external fluid reservoir would be filled with an amount of liquid in excess to that amount actually required. By bringing the fluid in the pipette tip into contact with the microfluidic device, flow is initiated. The flow rate is regulated by the flow-restriction element, so the desired volume can be achieved by controlling the amount of time that the pipette tip interacts with the microfluidic device. The pipette tip can then be removed from proximity with the microfluidic card to terminate the metering operation. The fluid will then flow until it has self-positioned itself

with its trailing meniscus at the position known as the capillary retention valve (CRV) denoted by numeral 830, where a restricted diameter operates to resist further flows.

[0057] Figure 6 shows the basic operation, in which a pipette 620 is brought into proximity to a unit cell in an array 610. When the projecting portion of the fluid touches the aperture, capillary force initiates flow from the pipette into the channel. The attraction may be aided by making the inner surface of the receiving channel one that is wetted by the fluid and the top surface 540 one that is not wetted. (This also reduces spillage.) The fluid passes into the channel and through the restriction aperture 605 in restriction member 602, which is sized to reduce the fluid flow so that a timed flow will be more accurate. After the specified time, which will depend on the fluid viscosity, the dimensions and surface properties of the pipette and receiving channels, including the restriction aperture and the desired volume to be transferred, the pipette is removed. The fluid settles with its upper (trailing) meniscus at the restriction aperture.

[0058] Figure 8A shows the initial approach of pipette 620 carrying fluid 650 with projecting fluid 655 to the cell 810,

which has aperture 820 with upper interior surface 822, top surface 815 and restriction aperture 832 in CRV 830. Below the restriction aperture, the inner surface 825 of liner 824 has a different (and greater) attraction for the fluid than the upper surface 822.

[0059] Figure 8B shows the projection of the projecting fluid 655 just touching the top of aperture 820.

[0060] In Figure 8C, the fluid is in the initial stage of transfer, with a lower meniscus 662 approaching the restriction aperture 832.

[0061] Figure 8D shows the stage after the lower meniscus has passed through the restriction aperture and is passing down the lower portion of aperture 820 (the storage reservoir) at a rate determined largely by restriction aperture 832.

[0062] Figure 8E shows the same structure after the pipette has been withdrawn, with drop 655 at the bottom of the pipette having been separated from the top surface 655'.

[0063] Figure 8F shows the structure shortly after, when more of the fluid has passed into the lower storage reservoir, with lower meniscus 664 having passed to a lower depth and an upper meniscus 672 having formed.

[0064] Lastly, Figure 8G shows the structure in its final state,

when the upper meniscus 672 has been pinned at the level of the restriction aperture.

[0065] The operation has been shown with a single vertical aperture for simplicity, but the U-shaped structure of Figure 4 or more complex structures may be used.

[0066] One area where these techniques are applicable is in the area of reagent storage. Useful reagent storage (whether for minutes or months) at small volumes is complicated by the difficulty of controlling the positioning of fluid within the storage container. When there is poor control over initial positioning of stored reagents, subsequent reactions of these reagents with additional reactants are not well controlled. According to the invention, microfluidic structures with integrated capillary-retention valves may be used for reagent storage. Using this method, reagents can be applied to the inlet port of a microstructure with relatively low precision, but can then be precisely driven by capillary action to move fluid to a predetermined position within the microstructure.

[0067] Referring again to Figure 6, the lower portion of the vertical channel may be used to store a reagent, with the trailing meniscus pinned to aperture 605 holding it in place. The vertical channel of Figure 6 can be part of a U-shaped

structure as in Figure 4 or of a more complex structure. The accurate positioning of the fluid enables one to calculate precisely the dynamics of a reaction so that it is reproducible and as designed. Such reagents stored in microstructures can also be held or frozen in situ for use at much later times.

[0068] The rinsing of fluids is an important step in many biochemical protocols. However, achieving reproducible rinsing at low liquid volumes is difficult; commercially, an inherently large footprint per test is currently required to achieve good results. The ability to perform multiple fluid rinses in a small footprint would be advantageous and a method to do so within a microstructure has been demonstrated in the literature. However, in that instance, a separate secondary structure is needed in order to enable fluid extraction (which drives the rinse process by a capillary-flow mechanism) from the primary fluid-processing microstructure. This requirement for a secondary component adds undesired complexity (e.g. alignment requirements) to practical implementations. According to the invention, a fully-integrated structure is able to perform rinsing and to enable multistep assays by using multilayer structures to significantly increase the volume

of the attached capillary-driven flow-promotion zone (esp. in the third dimension). Illustratively, an optional feature of Figure 6 is an additional set of greensheets denoted generally by dotted line 680 that adds a longer and deeper reservoir at the bottom of Figure 6.

[0069] This method allows for a small overall footprint, enables low-volume assays that are heterogeneous in nature, and helps to prevent spillover of unwanted reagent in the event that the microfluidic structure is composed of multiple parts and needs to be separated.

[0070] Similar microfluidic methods and structures can be used to precisely deliver biological cells and other non-fluid entities (such as beads or nanoparticles) carried in a non-homogenous fluid to a substrate. The substrate can, for example, be a wall of an assembled structure which can then be disassembled to allow substrate-specific processing. Also, reagents can be delivered to any such entities (e.g. cells, beads, nanoparticles, etc) that have been attached to a surface of the microchannel in an earlier step. As one example, culture media with biological cells can be delivered to a microstructure and positioned through the use of a capillary-retention valve. The biological cells can then settle to the bottom surface 125 of the microstruc-

ture (channel 126) in a predictable manner, where they are then to able attach themselves in a process similar to that found in conventional cell culture. Subsequent rinse and reagent application steps can then be used to perform valuable cell-based assays.

[0071] Conventional methods for low-volume reagent handling are generally very wasteful of reagents. This becomes especially problematic when a reagent is expensive and/or in short supply. Structures according to the invention use a microstructure with a height that is typically a reduced multiple of the diffusion constant (which must be at least roughly known) to minimize reagent that cannot interact with the surface. Additionally it provides for a designed flow using the techniques described above, such that in approximately the amount of time it takes for reagents to be depleted near the surface, a fresh supply of reagent can be introduced. This can be either continuous or quantized flow, but the design is intended to allow the most efficient application of reagent in the shortest time. The invention also includes use of microfluidic structures to write lines and spots in which a projecting drop such as 655 in Fig. 8A is brought into contact with the paper or other medium.

[0072] Referring now to Figure 5, there is shown the sequence of assembling an embodiment of the invention, in which Figure 5A shows three ceramic greensheets 502 stacked up, each greensheet containing a fugitive material 530 filling the site of a vertical aperture. At the bottom, sheet 505 contains a horizontal strip, also filled with material 530, that will become a horizontal channel connecting the two vertical apertures. Figure 5B shows the assembled stack, ready for firing and Figure 5C shows the assembly 510 after firing, with the U-shaped passage comprising the two vertical passages 535 and the horizontal passage 515.

[0073] In Figures 5D and 5E, two variants of a bottom plate are shown, with plate 520 in Figure 5D having a channel 522 formed into its upper surface and plate 520' in Figure 5E without a channel.

[0074] Figure 5F shows the combination of the assembly of Figure 5C with the bottom plate 520' of Figure 5E.

[0075] Figure 5G shows the assembly after an optional step of treating the top surface with a substance 540, illustratively to prevent a reagent from wetting the top surface and wasting reagent that will not pass into one of the apertures 535. Those skilled in the art will appreciate that other topologies are possible, for example that more than

one vertical aperture may be formed, that a restriction aperture such as that shown in Figure 6 may be included in one or both vertical apertures and that one or more vertical apertures may extend down below the horizontal aperture 515 for storage of rinsing fluid or excess reagent.

[0076] Figure 7 shows a sequence illustrating the use of differential wettability. Fig 7A shows a single aperture 708 in plate 710, having received a quantity of reagent dissolved in, for example, dimethylsulfoxide, DMSO, a conventional solvent Interior surface 702 of the aperture has been treated (or the material of block 710 has been chosen) to attract the DMSO through capillary force.

[0077] In contrast, as shown in Fig 7B, top surface 712 of block 710 is not wetted by water and water-based reagents will not penetrate into the channel. Fig 7C shows the administration of a water-based reagent from below, so that the fluid penetrates into the aperture from below. The volume of DMSO fluid has been chosen such that the lower meniscus 720 will be reached by the water-based reagent 717. As shown in Fig 7D, the two fluids meet and react in an overlap zone denoted by the dashed line in Fig 7D.

[0078] The parameters have been chosen such that the diffusion

distances of the reagents permit the reactants to reach one another.

[0079] Referring now to Figure 9A, there is shown a top view looking toward the x-y plane, of a holder according to the invention, in which a frame 150 holds the micro-plate. Frame 150 translates in the x and y directions as discussed below. On the left, box 135 represents a battery that supplies electrical power to actuators. Alternatively, box 135 could represent a storage unit for compressed gas for application to actuators and/or to the modules in the array to move fluids in or out.

[0080] Numeral 55 represents a ledge that holds the microplate. Numeral 52 denotes a large aperture that exposes the array of wells to operations implemented from below. Tubes 42 and 44 represent gas and vacuum lines. At the corners, boxes 120 represent position sensors for the measurement of alignment of the microplate.

[0081] Figure 9B shows a cross section of the holder of Figure 9A, in which plate 50 is shown as displaced from ledge 55. Lifting pins 45 represent a feature for raising the plate so that robotic material handlers can grip it. Lower frame 110 contains actuators described below for moving frame 150 in the x-y plane.

[0082] Figure 10 shows a detail of the interface between lower frame 110 and holding frame 150. On the right side, a pair of actuators 130 at the top and bottom are positioned between lower frame 110 and frame 150. Actuators 130 may be piezoelectric, screws controllable by commands from a controller not shown and pistons activated by compressed gas, etc. They push frame 150 to the left. Conventional springs or an elastomer on the left of the frame supply restoring force if needed. Optionally, the piezoelectric actuators can be bonded at both ends and will not need a restoring force. The same arrangement is repeated on the bottom. With this approach, the upper frame can be pushed in the x-y plane to a desired position. The contact surfaces against which the actuators push can be in the same plane as plate 50 or can be offset vertically, at the option of the designer.

[0083] Figure 11 shows a side view of an alternative embodiment of the invention, in which a second ledge 65 positioned above ledge 55, holds an array of microlenses used for optical examination of the results of the combination of test specimen and reagent in the wells. The lenses can focus light on the fluids under test and can also deliver signal light to a commercially available optical device.

[0084] The dotted line 75 at the bottom represents an optional lower lens array.

[0085] A distribution/operation system can be used to process the microfluidic arrays. In Figure 12, there is shown in general form an array of units matching the well array and containing a set of rows 72-1 - 72-n that contain alternating units represented by circles 77 and boxes 78. A set of heavy lines 73-1 - 73-n represent a distribution system for pressure and/or vacuum. The circular and rectangular symbols 77 and 78, respectively, are used to point out that it is not necessary according to the invention that all units be the same. For example, the boxes could represent a chamber as denoted in Figure 3 for receiving surplus fluid after a rinsing operation and the boxes could represent a pressure source with individual valve control for applying pressure to the bottom of a module 310 as shown in Fig. 3. As another option, the circles could represent micro-lenses as in Fig. 6, and the boxes represent pressure / vacuum supply.

[0086] The plate being processed could have wells that only use one of the two options (or could have a standard array with only half the wells being used for this particular operation). Alternatively, the frame 150 could be translated

by the actuators (with the plate optionally being lifted vertically to slide without making contact with the lower array), so that in a first operation, half the wells are processed by circles 77, say, the plate is translated and, in the second operation, the second half of the wells are processed. The two-step process could then be repeated using the devices represented by the rectangles. Alternatively, a first half of the array could be processed with both the circles and rectangles and then the second half.

[0087] Referring to Figure 13, there is shown an exploded view of the interface between a module 310, as shown in Figure 3, and the distribution / operation system. In this version, unit 310 has a projecting cylindrical nozzle 317 having a bottom surface 315 and enclosed by wall 310. Below, the support system represented by dotted line 680 in Figure 6, has a cylinder 385 with an inner surface 384 and top surface 382. Axis 82 denotes that the two cylinders have a common center. In one embodiment, surface 315 presses against surface 382, with wall 310 projecting past the point where the surfaces meet to confine any spray that may result. In another embodiment, inner surface 384 may enclose the projecting cylinder 317, so that there is vertical overlap. Gas pressure, vacuum or reagents may be

supplied from cylinder 385 into the module or may be removed, e.g. a vacuum may be used to draw unused reagent out of the cell, with the result of the reaction either having been determined by optical means or by depositing on the inner wall of cylinder 315, to be tested in a later step. Instead of a cylinder, a wide flat surface as shown in Figure 6 may be used.

[0088] Those skilled in the art will appreciate that the reagent can be urged against the reacting surface (or other reagents in the form of non-homogeneous substances such as microparticles, microbeads, nanoparticles or biological cells) by the application of an external force such as gravity, electrophoretic force or electroosmotic force.

[0089] While the invention has been described in terms of a single preferred embodiment, those skilled in the art will recognize that the invention can be practiced in various versions within the spirit and scope of the following claims.

[0090] What is claimed is: